REMARKS

This responds to the Office Action mailed on February 26, 2009.

Claim 55 is canceled, and claims 6 and 51 are amended. Claim 59 is added; as a result, claims 6, 10-14, 44-53, 56 and 59 are now pending in this application.

Claim 6 is amended solely to focus the issue to be resolved in addressing the obviousness rejection. The amendment to claim 6 is further supported by claim 55 and by Example 4.

New claim 59 is supported by Example IV. As claimed, Applicants' invention is the new use of an "old composition," namely of the glutamine-carbohydrate compositions disclosed in commonly-assigned Shinal et al. (PCT WO/2000/69470) as "Aesgen-14" or "AES-14." When orally administered to a breast cancer patient undergoing radiation therapy, the compositions protect normal tissue remote from the tissue of the gastrointestinal (g.i.) tract of the patient, such as breast tissue and associated upper-body tissue, such as the skin, from the deleterious and painful effects of the radiation. Such effects include increased breast density, edema and outward appearance. Amended claim 6 is supported by the clinical study reported in Example 4.

Although at page 6 of the Office Action, the Examiner suggests that the recited effects were inherent in the practice of the cited art, as opposed to the ability of the compositions to protect mucosal tissue, the Examiner has provided not one iota of factual evidence that this beneficial effect ever occurred. Furthermore, none of the cited documents disclose the administration of a composition comprising glutamine and carbohydrate to a subject afflicted with breast cancer. Thus, there was no situation were the effect would have occurred. Applicants respectfully submit that inherency, if used as the basis of an anticipation rejection, must be certain, whether or not it was appreciated by the art. Ex parte McQueen, 123 USPQ 37 (Bd. App. 1958); Glaxo, Inc. v. Novapharm. Ltd., 52 F.3d 1043 (Fed. Cir. 1995); Perricone v. Medicis, 423 F.3d 1368 (Fed. Cir. 2005). Since the Examiner has failed to meet the burden of establishing that the present claims are anticipated under 35 U.S.C. § 102(b), Applicants will confine themselves to addressing the obviousness rejection that the Examiner has advanced against the claims.

§ *103 Rejection of the Claims*

Claims 6, 10-14, 44-53 and 55-56 were rejected under 35 U.S.C. § 103(a) as being obvious over Skubitz et al. (U.S. Patent No. 5,545,668; hereinafter "Skubitz") in view of Shinal et al. (PCT Publication No. WO 00/69470; hereinafter "Shinal") and Klimberg et al. (Am. J. Surg., 1996, vol. 172, pp. 418-424; hereinafter "Klimberg"). This rejection is respectfully traversed.

As noted above, Applicants concede that both Skubitz and Shinal disclose orally-administerable aqueous glutamine-containing compositions. As noted by the Examiner, Skubitz discloses that oral administration of these compositions can reduce "oropharyngeal mucositis" (mucositis of the mucous membranes of the pharnyx or mouth) (Skubitz at Abstract); col. 4, lines 1-19), due to chemotherapy or radiation. Both Skubitz and Shinal disclose aqueous compositions comprising glutamine, sucrose, glycerin and sorbitol. One such composition is disclosed in Example 1 of Skubitz. A similar aqueous composition is disclosed in Shinal as Aesgen-14 or AES-14. See Table 1. As noted by the Examiner, Shinal disclose that AES-14 can substantially increase the gastrointestinal uptake of glutamine, which is the target tissue for the protective effects of the glutamine.

Applicants also agree that Skubitz does not teach oral glutamine and carbohydrate can or should be orally administered to a breast cancer patient so as to protect normal breast and upper-body tissue from the deleterious effects of radiation therapy. Also, Shinal does not disclose or suggest this utility for AES-14. In an attempt to remedy this deficiency in Skubitz and Shinal, the Examiner has cited Klimberg et al., Am. J. Surg., 172, 418 (1996) as reviewing literature allegedly disclosing that the administration of glutamine, given alone, "makes tumor cells more sensitive to radiation and chemotherapy while at the same time [restores] depressed levels of GSH in normal tissues, thereby improving the overall well-being and resulting in decreased morbidity and mortality associated with cancer and its treatment (paragraph bridging pages 423 and 424)." Klimberg et al. is also cited for the general statement: "when given with radiation therapy or chemotherapy, glutamine protects the host and actually increases the selectivity of therapy for the tumor" (p. 418).

However, the Examiner is requested to note that Klimberg et al., and the literature cited therein, as well as other publications appearing prior to the filing date of the present application

do not remedy the deficiencies in Skubitz and Shinal, even when viewed in hindsight. The Examiner is respectfully requested to note that the glutamine-carbohydrate composition is being administered to protect normal tissue, such as skin, from the direct effects of radiation, not for the purpose of treating the cancer, in the sense of inhibiting its spread. Treatment claims, such as 1, 39 and 41, were cancelled and claim 6 has been amended to recite the protective effect of the present compositions.

The Examiner is requested to note that the art worker, in possession of the literature available in 2003, would not be apprised that glutamine, administered orally or intravenously as a single agent, would have any effect on the integrity of mucosa tissue subjected to radiation or chemotherapy much less tissue remote from the g.i. tract, such as normal breast tissue and associated upper body tissue, including skin.

While the Examiner has accepted Applicants' arguments as presented in the last amendment regarding the deficiencies of the Wilmore et al. patent, the Examiner is requested to note that Wilmore published the clinical results that his group attained in 1992 as F.R. Ziegler et al., "Clinical and Metabolic Efficacy of Glutamine-Supplemental Parenteral Nutrition after Bone Marrow Transplantation," Annal. Int. Med., 116, 821 (1992) (of record). This paper is cited as ref. 38 in Klimberg et al. at page 423 as "perhaps the best" clinical trial in human patients, and relied upon by the Examiner. The authors reported the results for 24 glutamine-supplemental patients and 21 control patients. Both groups were treated while recovering from BMT (40/45 patients received total body radiation). While the glutamine-supplemented patients had some improved clinical parameters, there was no difference in their "Cumulative Mucositis Scores" (see Table 4). Thus, susceptible normal tissue was not protected by glutamine, following radiation.

These results were confirmed by P.R. Schloerb et al., J. Parent. Ent. Nutr., 17, 407 (1993) (of record) (ref. 37 in Klimberg et al.) who found no significant difference in oral mucositis between a group of 13 patients receiving standard TPN and 16 patients receiving glutamine-supplemented TPN (Table IV, page 410, Col. 1, lines 4-6), and by P.R. Schloerb et al., J. Parent. Ent. Nutr., 23, 117 (1999) (copy enclosed) who found no significant difference in sepsis or oral mucositis between a group of 35 BMT patients receiving oral glutamine and 31 patients receiving an oral control (Tables V and IV). Similar results were observed for high dose oral

glutamine versus controls by T. M. Dickson, J. Patent. Ent. Nutr., 24, 61 (2000) (copy enclosed), and by H.C.T. van Zaanen et al., Cancer, 74, 2879 (1994) (of record), who found that the glutamine analog, "glutamine dipeptide" had no effect on mucositis in patients undergoing chemotherapy. See Table IV. Thus, despite the promise offered by the rat studies summarized by Klimberg et al., glutamine administered parenterally or orally without high concentrations of carbohydrates, is not effective in protecting the normal mucosal tissue of patients subjected to radiation therapy.

The Examiner is requested to note that a reference which would lead one of ordinary skill in the art away from the claimed invention cannot render it unpatentably obvious. Dow Chem. Co. v. American Cyanamid Company, 2 USPQ 2d 1350 (Fed. Cir. 1987); In re Dow Chemical Co., 5 USPQ 2d 1529 (Fed. Cir. 1988); In re Grasseli et al., 218 USPQ 269 (Fed. Cir. 1983). One of ordinary skill in the art, in possession of all of the relevant art, would not be lead to expect that administration of glutamine by any route, would reduce damage to susceptible mucosal tissue in human cancer patients.

The Examiner is respectfully urged to consider that the animal studies summarized in Klimberg et al. and resummarized and relied upon by the Examiner do not relate to the protective effects of glutamine on normal, non-mucosal tissue of irradiated animals. While it is sometimes difficult to determine the citation in Klimberg et al. that matches the section of the review cited by the Examiner, the Examiner is respectfully requested to consider the following remarks regarding the additional literature cited in Klimberg et al. Klimberg et al., JPEN, 34 (1989) (citation incomplete) apparently discuss the ability of glutamine to protect the intestinal tract tissue of rats subjected to "whole abdominal radiation" in terms of "the jejunal villous number, villous height and the number of metaphase mitoses per crypt." (Klimberg et al. at page 419). This does not disclose or suggest that the present glutamine compositions would protect normal breast tissue and upper body tissue from injury due to radiation therapy for breast cancer. Likewise, Jensen et al., Annal. Surg. Oncol., 1, 157 (1994) (copy enclosed) reports that provision of oral glutamine to rats subjected to radiation to the bowel may have a protective effect against chronic radiation enteropathy of the small intestine. These results do not disclose or suggest that the present glutamine compositions would protect normal breast and upper body tissue of breast cancer patients undergoing radiation therapy (Klimberg et al., ref. 24, pages 419-420).

Hong et al., Annal. Surg., 215, 114 (1992) (copy enclosed) is another rat study from the Wilmore group that reports that glutamine supplemented TPN (given i.v.), reduces acetaminophen toxicity to the liver. The results of this study are not relevant to the protection of the normal breast and associated upper body tissues of breast cancer patients against radiation-induced damage such as edema and increased breast density (Klimberg et al., ref. 18, page 420). Likewise, the results reported by Klimberg et al. at page 420 (summarizing a paper given by Klimberg et al., ref. 26), report increased "tumor kill" in rats implanted with MCA sarcomas, administered glutamine and irradiated. Claim 6 is not directed to the ability of glutamine to increase tumor sensitivity to radiation, but to protect normal non-mucosal tissues of breast and upper body of breast cancer patients against the effects of radiation. The Examiner is requested that the results reported at page 420, last five lines, did not show improved efficacy of radiation after provision of glutamine. No tissue effects are reported in Klimberg et al.

To connect glutamine to breast cancer, the Examiner relies on a section of Klimberg et al. (pages 422-423), in which glutamine fed to rats implanted with MTF-7 breast cancer cells responded better when treated with methotrexate [?]. This study is not referenced and the account is incomplete. The results reported do not disclose or suggest that glutamine would protect normal breast and associated upper body tissue of human breast cancer patients against radiation therapy-induced injury. In fact, page 422 of Klimberg et al. does not discuss preservation of any tissue from damage by chemotherapy.

The final reference relied upon by the Examiner as cited in Klimberg et al. is, in fact, the 1992 paper by Ziegler et al. (ref. 38 in Klimberg et al.). As discussed above, this reference discloses that glutamine had no effect on mucositis scores.

To summarize, all but one of the voluminous indirect citations relied upon by the Examiner from Klimberg et al. report rat studies in which the intestinal tissue of the rats subjected to abdominal radiation was protected to some extent, or "tumor kill" by chemotherapy was enhanced, by oral or i.v. glutamine. Hong et al. reports use of glutamine to protect the rat liver against the toxicity of a single chemical agent, not radiation. The "closest prior art" relied upon by the Examiner is apparently Jensen et al. which relates to the ability of glutamine to protect the rat bowel, a mucosal tissue, from radiation enteropathy.

As discussed above, later clinical studies on human patients subjected to radiation prior to BMT do not show a significant protective effect of glutamine on susceptible mucosa, e.g., g.i. tissues. The Examiner is respectfully requested to consider that it is error to selectively rely on prior art that allegedly supports the obviousness of the claimed invention, while ignoring more relevant references that teach away from the invention. In re Marshall, 538 F.2d 301 (CCPA 1978), In re Mercier, 515 F.2d 1161 (CCPA 1975).

Therefore, it is respectfully submitted that the cited references, either alone or taken in combination, do not render the presently claimed invention obvious. Thus, withdrawal of this rejection is appropriate and Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' representative at (612) 373-6905 to facilitate prosecution of this application.

If necessary, please charge any additional fees or deficiencies, or credit any overpayments to Deposit Account No. 19-0743.

Respectfully submitted,

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 373-6905

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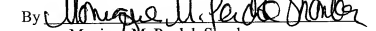
By 
Monique M. Perdok Shonka
Reg. No. 42,989

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/ Jonathan Ferguson /

Jonathan Ferguson